

AMENDMENTS TO THE SPECIFICATION

Please replace the title on page 1 of the specification with the following:

METHODS OF IMPROVING HEALTH-RELATED QUALITY OF LIFE IN INDIVIDUALS WITH SYSTEMIC LUPUS ERYTHEMATOSUS BY ADMINISTERING DOUBLE-STRANDED DNA EPITOPES

Please replace paragraph [0010] beginning on page 3 with the following:

[0010] In one aspect, the invention provides a method of stabilizing or improving the health-related quality of life in an individual with systemic lupus erythematosus (SLE), comprising administering to the individual an effective amount of a dsDNA epitope which specifically binds to an SLE-associated antibody (generally, an antibody which specifically binds to double-stranded DNA (an anti-dsDNA antibody), although as is known in the art, and described herein, such antibodies may also bind single-stranded DNA and/or mimetics or analogs of double-stranded DNA) from the individual, wherein the administration of the dsDNA epitope results in a stabilization of or improvement in the individual's health-related quality of life. In some embodiments, the dsDNA epitope is administered such that there is a sustained reduction of anti-dsDNA antibodies in the individual, wherein the sustained reduction is at least about 10% below baseline in the individual (for example, a value of 100 at baseline would drop at least about 10% to about 90). In some embodiments, the sustained reduction is for at least about one month, at least about two months, at least about three months, at least about 16 weeks (at least about four months), at least about five months, at least about 24 weeks (at least about 6 months), at least about 48 weeks, or at least about one year. In some embodiments, the sustained reduction is for at least about two years or longer. Ideally, treatment results in a sustained reduction for years, since SLE is a chronic disease. In some embodiments, the dsDNA epitope is the double-stranded polynucleotide 5'-GTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1) 5'-TGTGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1) in combination with its complementary strand, particularly the sequence 3'-CACACACACACACACACA-5' (SEQ ID NO:2) 5'-CACACACACACACACACA-3' (SEQ ID NO:2), or one of the single-stranded polynucleotides 5'-GTGTGTGTGTGTGTGTGTGT-

~~3'-(SEQ ID NO:1) 5'-TGTGTGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1) or 3'-CACACACACACACACACACA-5'-(SEQ ID NO:2) 5'-CACACACACACACACACACA-3' (SEQ ID NO:2).~~ The dsDNA epitope is optionally administered in the form of an epitope-presenting carrier. In some embodiments, the stabilization or improvement in the individual's health-related quality of life occurs before, during, or after a renal flare. In some embodiments the dsDNA epitope is administered to the individual for more than about 16 weeks.

Please replace paragraph [0013] on page 6 with the following:

[0013] In some embodiments, the level of circulating SLE-associated antibodies in the individual is reduced by administration of an effective amount of a dsDNA epitope, such as the double-stranded polynucleotide ~~5'-GTGTGTGTGTGTGTGTGTGTG-3'-(SEQ ID NO:1)-5'-TGTGTGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1)~~ and its complementary strand, particularly the sequence ~~3'-CACACACACACACACACACA-5'-(SEQ ID NO:2)-5'-CACACACACACACACACACA-3' (SEQ ID NO:2)~~ or one of the single-stranded polynucleotides ~~5'-GTGTGTGTGTGTGTGTGTGTG-3'-(SEQ ID NO:1)-5'-TGTGTGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1) or 3'-CACACACACACACACACACA-5'-(SEQ ID NO:2)-5'-CACACACACACACACACACA-3' (SEQ ID NO:2)~~ to the individual. In another embodiment, the invention provides a method of stabilizing or improving the health-related quality of life of an individual with SLE, comprising reducing the level of circulating SLE-associated antibodies in the individual by administering to the individual an effective amount of an epitope-presenting valency platform molecule, such as LJP 394. In some embodiments, administration of an effective amount of the dsDNA epitope results in a sustained reduction of anti-dsDNA antibodies in the individual, wherein the sustained reduction is at least about 10% below baseline in the individual. In some embodiments, the sustained reduction is for at least about one month, at least about two months, at least about three months, at least about 16 weeks (at least about four months), at least about five months, at least about 24 weeks (at least about 6 months), at least about 48 weeks, or at least about one year. In some embodiments, the sustained reduction is for at least about two years or longer. Ideally, treatment results in a sustained reduction for years. In some embodiments, the stabilization

or improvement in the individual's health-related quality of life occurs before, during, or after a renal flare.

Please replace paragraph [0066] beginning on page 16 with the following:

[0066] We have discovered that administration of a dsDNA epitope that binds to SLE-associated antibodies, namely a conjugate comprising a non-immunogenic platform molecule and four double-stranded DNA epitopes, namely, LJP 394 (having four double-stranded DNA molecules with the sequence ~~5'-GTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1))~~ 5'-TGTGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1)), to systemic lupus erythematosus (SLE) patients effected improvement in the health-related quality of life of the patients, especially and notably among the subpopulation of patients having sustained reductions of anti-dsDNA levels and in those patients experiencing documented renal flares (with the positive effects occurring both prior to and following the occurrence of the renal flares). This result of stabilization or improvement in the health-related quality of life (HRQOL) of the patients, even in aspects of HRQOL that are dictated by emotional and mental health, and across various patient subpopulations, was surprising and unexpected.

Please replace paragraph [0070] beginning on page 19 with the following:

[0070] Accordingly, in one aspect, the invention provides a method of stabilizing or improving the health-related quality of life in an individual with systemic lupus erythematosus, comprising administering to the individual an effective amount of a dsDNA epitope which specifically binds to an SLE-associated antibody from the individual (generally, an antibody which specifically binds to double-stranded DNA (anti-dsDNA antibody), although as is known in the art, and described herein, such antibodies may also bind single-stranded DNA and/or analogs or mimetics of double-stranded DNA), wherein the administration of the dsDNA epitope results in a stabilization of or improvement in the individual's health-related quality of life. In some embodiments, the effective amount of dsDNA epitope is administered to the individual for a period of more than about 16 weeks. In some embodiments, the dsDNA epitope is administered such that

there is a sustained reduction of anti-dsDNA antibodies in the individual, wherein the sustained reduction is at least about 10% below baseline in the individual for greater than or equal to about 2/3 of all observed values prior to HDCC treatment or the last (most recent) dose of a drug (for example, LJP394) used for treatment or about 2/3 of all values measured during treatment. (The term “baseline” refers to the mean of the last two determinations of the circulating anti-dsDNA antibody level in an individual prior to initial administration of the drug. A baseline may also be established by a measurement of anti-dsDNA antibodies prior to, or upon, initial administration of the drug.) In some embodiments, the sustained reduction is maintained for more than about 16 weeks. In other embodiments, the sustained reduction is maintained for more than about 24 weeks. In some embodiments, the sustained reduction is for at least about one month, at least about two months, at least about three months, at least about 16 weeks, at least about four months, at least about five months, at least about 24 weeks, at least about 6 months, at least about 48 weeks, or at least about one year. In some embodiments, the sustained reduction is for at least about two years or longer. Ideally, treatment results in a sustained reduction for years, since SLE is a chronic disease. In further embodiments, the epitopes are attached to valency platform molecules. In some embodiments, the dsDNA epitope is administered to the individual in the form of a conjugate comprising (a) a non-immunogenic valency platform molecule and (b) two or more double-stranded DNA (dsDNA) epitopes, wherein the administration of the dsDNA epitope results in a stabilization of or improvement in the individual’s health-related quality of life. In some embodiments, the dsDNA epitope comprises, consists essentially of, or consists of the double-stranded polynucleotide ~~5’-GTGTGTGTGTGTGTGTGTGT-3’ (SEQ ID NO:1)~~ 5’-TGTGTGTGTGTGTGTGTGTG-3’ (SEQ ID NO:1) and its complementary strand, particularly the sequence ~~3’-CACACACACACACACACA-5’ (SEQ ID NO:2)~~ 5’-CACACACACACACACACA-3’ (SEQ ID NO:2), or one of the single-stranded polynucleotides ~~5’-GTGTGTGTGTGTGTGTGTGT-3’ (SEQ ID NO:1)~~ 5’-TGTGTGTGTGTGTGTGTGTG-3’ (SEQ ID NO:1) or ~~3’-CACACACACACACACACA-5’ (SEQ ID NO:2)~~ 5’-CACACACACACACACACA-3’ (SEQ ID NO:2). In still another embodiment, the conjugate is LJP 394. In some embodiments, the stabilization or improvement in the individual’s health-related quality of life occurs prior to or following a renal flare. In some embodiments, the method is a method of stabilizing the health-

related quality of life of an individual with SLE. In some other embodiments, the method is a method of improving the health-related quality of life of an individual with SLE.

Please replace paragraph [0122] beginning on page 40 with the following:

[0122] In another aspect, the invention provides a method of stabilizing or improving the health-related quality of life of an individual with systemic lupus erythematosus, comprising reducing the levels of circulating SLE-associated antibodies in the individual, wherein reducing the levels of circulating SLE-associated antibodies in the individual results in a stabilization of or improvement of the individual's health-related quality of life. In some embodiments, the method comprises the administering to the individual an effective amount of an agent that reduces SLE-associated antibodies in the individual. In another embodiment, the agent is administered to the individual such that there is a sustained reduction in the individual's anti-dsDNA antibody level of at least about 10% below baseline for greater than or equal to about 2/3 of all observed values prior to HDCC treatment or the last (most recent) dose of a drug (for example, LJP394) used for treatment or about 2/3 of all values measured during treatment. In some embodiments, the sustained reduction is for at least about one month, at least about two months, at least about three months, at least about 16 weeks, at least about four months, at least about five months, at least about 24 weeks, at least about 6 months, at least about 48 weeks, or at least about one year. In some embodiments, the sustained reduction is for at least about two years or longer. Ideally, treatment results in a sustained reduction for years, since SLE is a chronic disease. In some embodiments, the SLE-associated antibodies in the individual are antibodies that specifically bind double-stranded DNA and/or single-stranded DNA. In some embodiments, the SLE-associated circulating antibodies bind either strand or both strands of the double-stranded polynucleotide comprising, consisting of, or consisting essentially of a strand having the sequence ~~5'-GTGTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1)~~ 5'-TGTGTGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1) and the complementary strand ~~3'-CACACACACACACACACA-5' (SEQ ID NO:2)~~ 5'-CACACACACACACACACA-3' (SEQ ID NO:2). Optionally, the SLE-associated antibodies bind one of the single-stranded polynucleotides ~~5'-GTGTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1)~~ 5'-TGTGTGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1) or ~~3'-CACACACACACACACACA-5' (SEQ ID NO:2)~~ 5'-CACACACACACACACACA-3' (SEQ ID NO:2).

~~5'-(SEQ ID NO:2) 5'-CACACACACACACACACA-3' (SEQ ID NO:2).~~ In some embodiments, the sustained reduction of anti-dsDNA antibodies in the individual is at least about 20% or at least about 30% from baseline.

Please replace paragraph [0213] on page 72 with the following:

[0213] In preferred embodiments, the affinity of the individual's antibodies for the dsDNA epitope(s) (whether measured directly using the epitope itself or using a moiety/epitope the affinity of which may be correlated to the affinity of the epitope used in the carrier) is measured as the apparent equilibrium dissociation constant (K_D) for the dsDNA epitope(s) in the carrier before or upon initiation of treatment is less than about (in some embodiments, less than or equal to about) 1.0 mg IgG per mL. In other embodiments, the K_D is less than about (in some embodiments, less than or equal to about) any of the following: 0.8; 0.7; 0.6; 0.5; 0.4; 0.3; 0.2; 0.1; 0.09; 0.08; 0.07; 0.06; 0.05; 0.025. In some embodiments, K_D is less than about (in some embodiments, less than or equal to about) 0.8 mg IgG per mL. In some embodiments, K_D is less than or equal to about (in some embodiments, less than or equal to about) 0.5 mg IgG per mL. In some embodiments, K_D is less than about (in some embodiments, less than or equal to about) 0.1 mg IgG per mL. In some embodiments, the dsDNA epitope used comprises, consists essentially of, or consists of the double-stranded polynucleotide ~~5'-GTGTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1) 5'-TGTGTGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1)~~ in combination with its complementary strand, particularly the sequence ~~3'-CACACACACACACACACA-5' (SEQ ID NO:2) 5'-CACACACACACACACACA-3' (SEQ ID NO:2)~~, or one of the single-stranded polynucleotides ~~5'-GTGTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1) 5'-TGTGTGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1)~~ or ~~3'-CACACACACACACACACA-5' (SEQ ID NO:2) 5'-CACACACACACACACACA-3' (SEQ ID NO:2)~~, and the initial K_D is less than about 0.8 mg IgG per ml (in some embodiments, less than or equal to 0.8 mg IgG per ml). In some embodiments, the therapeutic moiety is LJP 394.

Please replace paragraph [0231] on page 79 with the following:

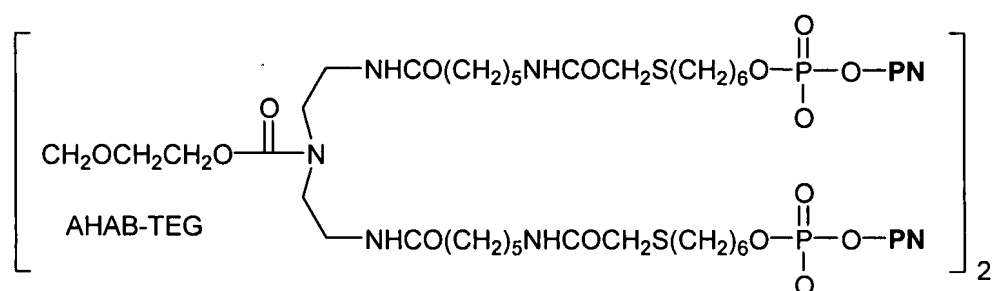
[0231] For instance, optionally, the polynucleotide is double-stranded DNA. In some embodiments, the polynucleotide comprises, consists essentially of, or consists of the double-stranded sequence ~~5'-GTGTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1)~~ 5'-TGTGTGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1) in combination with the complementary polynucleotide sequence, particularly the sequence ~~3'-CACACACACACACACACACA-5' (SEQ ID NO:2)~~ 5'-CACACACACACACACACACA-3' (SEQ ID NO:2).

Please replace paragraph **[0232]** on page 79 with the following:

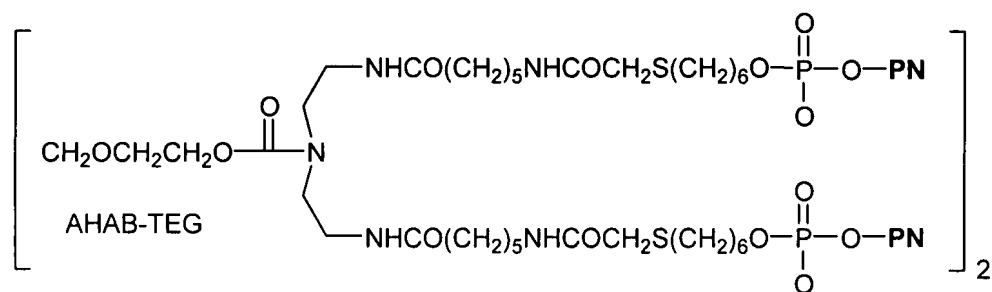
[0232] In some embodiments, the polynucleotide is single-stranded DNA comprising, consisting essentially of, or consisting of the sequence ~~5'-GTGTGTGTGTGTGTGTGTGTGT-3' (SEQ ID NO:1)~~ 5'-TGTGTGTGTGTGTGTGTGTGTG-3' (SEQ ID NO:1). In some alternative embodiments, the polynucleotide is single-stranded DNA comprising, consisting essentially of, or consisting of the sequence ~~3'-CACACACACACACACACACA-5' (SEQ ID NO:2)~~ 5'-CACACACACACACACACACA-3' (SEQ ID NO:2).

Please replace paragraph **[0277]** beginning on page 94 with the following:

[0277] A description of the synthesis of the conjugate LJP 394, a tetravalent conjugate, is described in Jones et al. (1995) and in U.S. Patent 5,552,391, which are hereby incorporated by reference. LJP 394 comprises four 20-mer oligonucleotides consisting of alternating C and A nucleotides, (CA)₁₀ 5'-(CA)₁₀-3' (SEQ ID NO:2), attached to a platform and annealed with complementary 20-mer oligonucleotides consisting of alternating G and T nucleotides, 5'-(TG)₁₀-3' (SEQ ID NO:1), oligonucleotide. The valency platform molecule used in LJP 394 is shown immediately below. In some embodiments, the platform molecule is



wherein PN is the polynucleotide. Accordingly, the epitope-presenting valency platform molecule administered to individuals with SLE in some embodiments of any of the methods of the invention described herein is LJP394 (also referred to herein as “Riquent”TM), which comprises a molecule of the following formula:



wherein PN is $(\text{CA})_{10} \bullet (\text{TG})_{10} ((\text{SEQ ID NO:2}) \bullet (\text{SEQ ID NO:1}))$. In some embodiments, pharmaceutically acceptable salts (e.g., sodium salts) of the molecules described herein are administered to individual with SLE. A variety of pharmaceutically acceptable salts are known to those of ordinary skill in the art.